Bioequivalence of Nanomedicines:

The need for novel bioanalytical approaches

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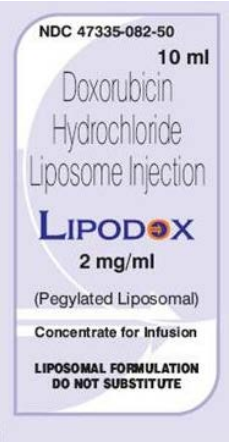
Nanomedicine

The First Nanomedicine generic

- Lipodox, a generic version of Doxil, was the first generic nanomedicine approved by the FDA (2013).
- Lipodox has not been approved by the EMA.



Nanomedicines are complex formulations, and there will always be some degree of polydispersity and batch-to-batch variation. For generic versions, the challenge is to identify meaningful differences between the follow-on and the reference/innovator product.

More Nanomedicine generics are Coming

- Azaya has bioequivalence study underway now with a generic Doxil formulation, ATI-0918.
- Sorrento Therapeutics also has an ongoing bioequivalence study for a nab-paclitaxel alternative IG-001.

AZAYA THERAPEUTICS

SORRENTO THERAPEUTICS

As the number of FDA-approved nanomedicines continues to grow, the importance of developing a framework for evaluation of follow on versions of these treatments becomes increasingly important.

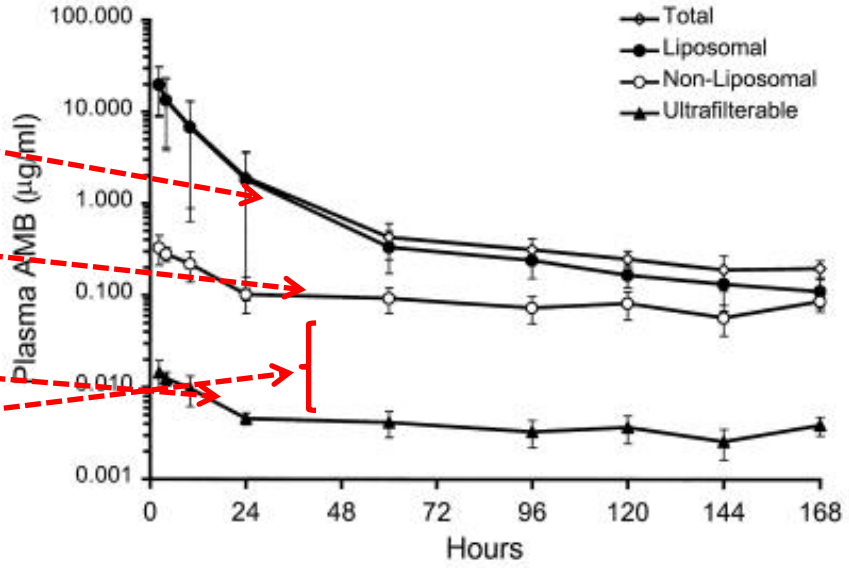
Nanomedicine Pharmacokinetics

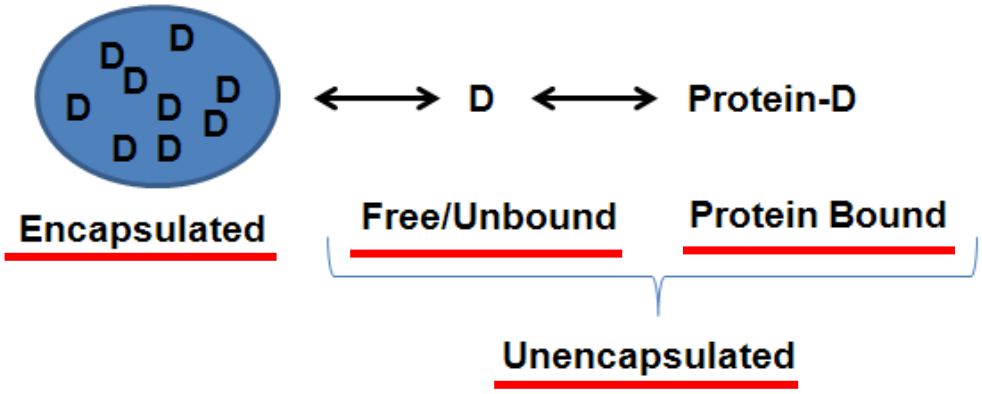
Nanomedicine Drug fractions in the circulation:

I. NM encapsulated fraction

II. Unencapsulated fraction

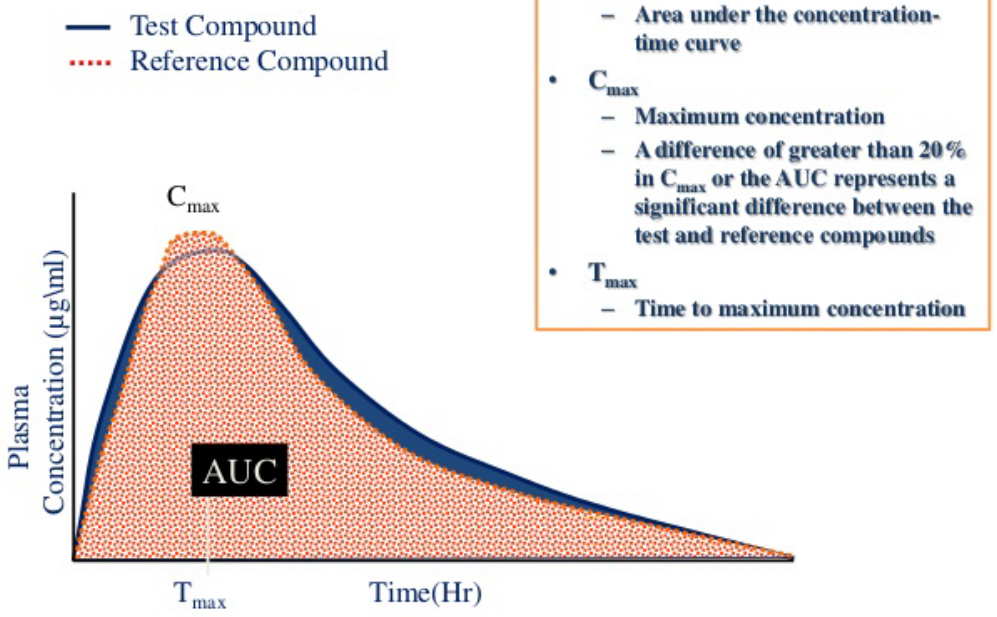
- fu : unbound fraction
- 1-fu: protein bound fraction



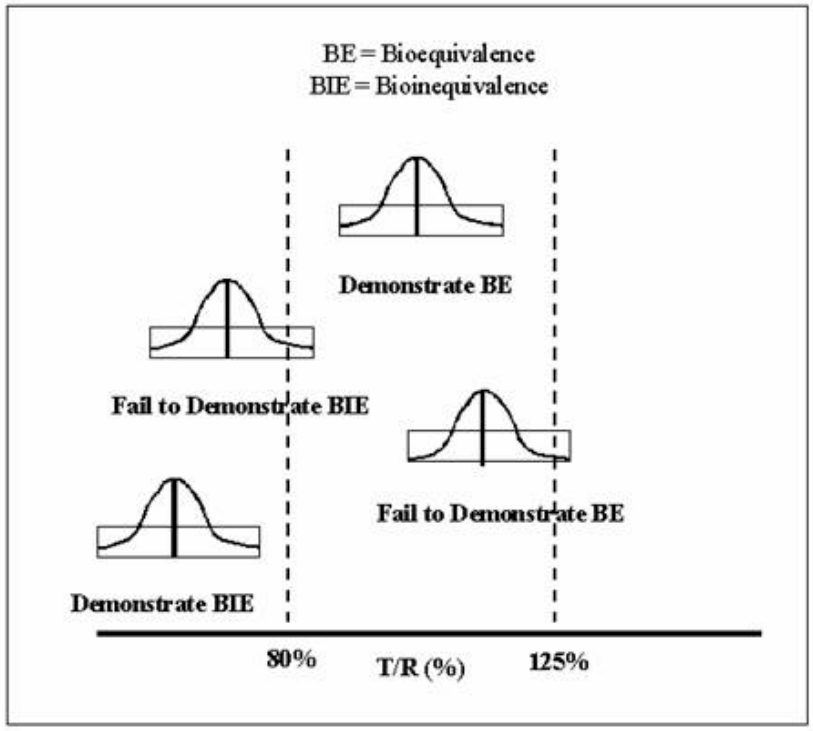


Bekersky et. al, *Antimicrob Agents Chemother* 2002, 46(3):834-40.

Nanomedicine Bioequivalence



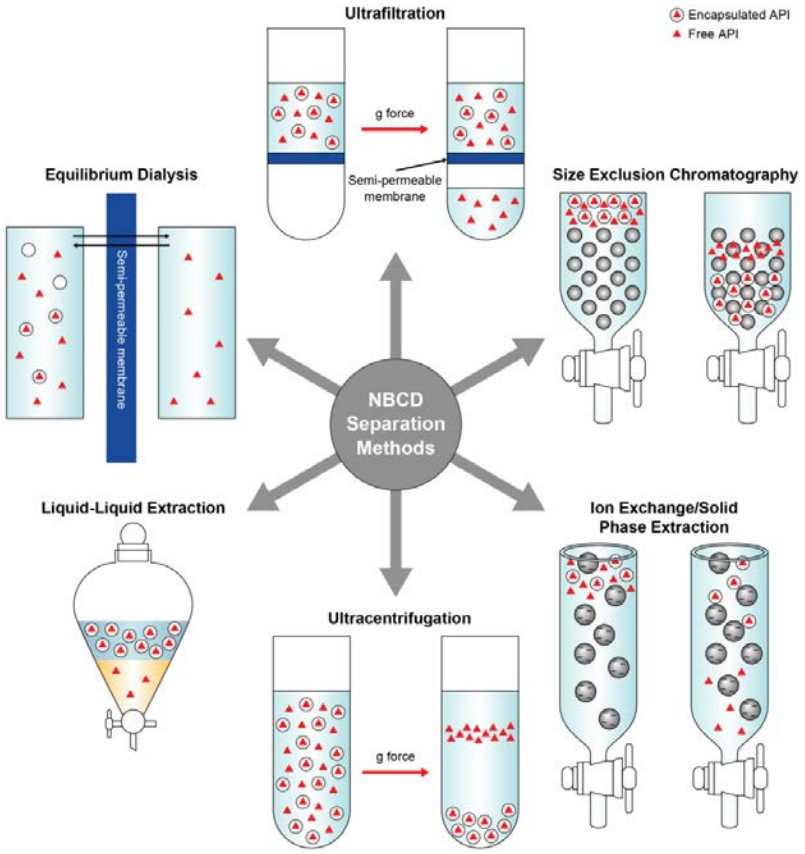
- **AUC**
  - Area under the concentration-time curve
- **C_{max}**
  - Maximum concentration
  - A difference of greater than 20% in C_{max} or the AUC represents a significant difference between the test and reference compounds
- **T_{max}**
  - Time to maximum concentration

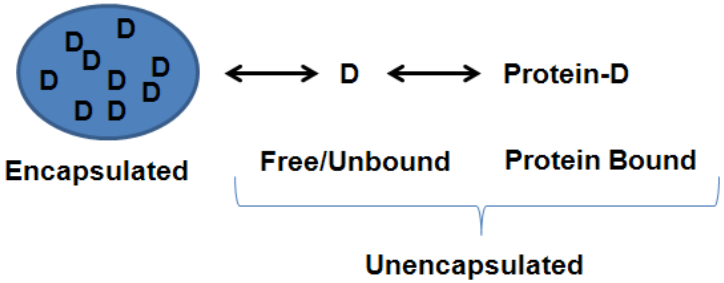


As per EMA/FDA guidance, nanomedicine bioequivalence is based on PK of total, unencapsulated and encapsulated drug fractions.

NBCD Pharmacokinetics and Bioanalytical Methods to Measure Drug Release. In Daan Crommelin D and de Vlieger J (ed) Non-Biological Complex Drugs; the science and regulatory landscape. Springer, New York, NY; 2015: In-press.

Existing Fractionation Methods





Main Problems

- Process induced artifacts
- Difficult to accurately differentiate protein bound and encapsulated API

Current methods have inherent flaws, adding inaccuracy and variability to nanomedicine fraction quantitation

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Case Study: Sun Pharma's Lipodox Bioequivalence Study

Study ID	Dose/patient population	Reference product	Number analysed (n)
PKD/08/038	50mg/m^2 ovarian cancer	Caelyx (Europe)	23
PKD/09/031	30mg/m^2 multiple myeloma	Caelyx (Europe)	26
PKD/09/030	50mg/m^2 ovarian cancer	Doxil (US)	41

- From Doxil comparison study report: 'Expecting +/- 5 % variation in T/R Ratio with expected intra subject CV of around 22.5 %, 24 subjects were required to prove bioequivalence. However based on the variability of free doxorubicin sample size was increased from 24 to 36 evaluable subjects in order to improve the result and meet the BE criteria for free doxorubicin…'

- From the EMA Assessment report: Free (un-encapsulated) doxorubicin is comparable, within 80.00-125.00% to Doxil (US reference product), but not Caelyx. This may be due to insufficient power of the Caelyx studies.

Ref: European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP) (2011a) CHMP Assessment Report: Doxorubicin Sun.

Sources of Intra-Subject Variability

- From the EMA Assessment report: The intra-subject variability for the encapsulated and total drug was CV <24%, while variability for the free/unencapsulated drug was 30-60%.
- Intra-subject variability >30% is considered highly variable

Ref: The AAPS Journal, Vol. 10, No. 1, March 2008 (# 2008)

Sources of intra-subject variability in crossover design:

- Biological considerations
- Errors in parameter estimates (e.g., AUC, Cmax)
- Measurement of drug concentrations

A likely source of unencapsulated variability

Ref: Sample Size Calculations in Clinical Research, Second Edition
By Shein-Chung Chow, Hansheng Wang, Jun Shao

In Summary

- The lack of robust nanomedicine fractionation methods are an impediment to both nanomedicine characterization and nanomedicine generic development
- Higher quality pharmacokinetic data will decrease patient sample size and facilitate regulatory determination of bioequivalence
- The FDA should support development, validation, implementation and harmonization of novel nanomedicine fractionation methods